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SYNTHETIC STUDIES OF YESSOTOXIN: ITERATIVE SYNTHESIS OF THE AB RING SYSTEM VIA Pd(II)-CATALYZED CYCLIZATION OF ALCOHOL

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Abstract – We report an iterative synthesis of the AB ring system of yessotoxin by using the Pd(II)-catalyzed cyclization reaction, as an approach towards a total synthesis.

Marine dinoflagellates produce many natural products, including polyethers, with unique structures and biological activities. Yessotoxin is a polyether isolated from the digestive glands of the scallop *Patinopecten yessoensis* (Figure 1).[1] Because of its complex structure and biological activities, which include the cytotoxicity and modulation of cytosolic calcium level in human lymphocytes, yessotoxin has attracted the attention of synthetic chemists.[2] We have been studying the Pd(II)-catalyzed stereoselective cyclization reaction of urethane and alcohol,[3] and herein we describe the application of this reaction for iterative synthesis of the AB ring system of yessotoxin.

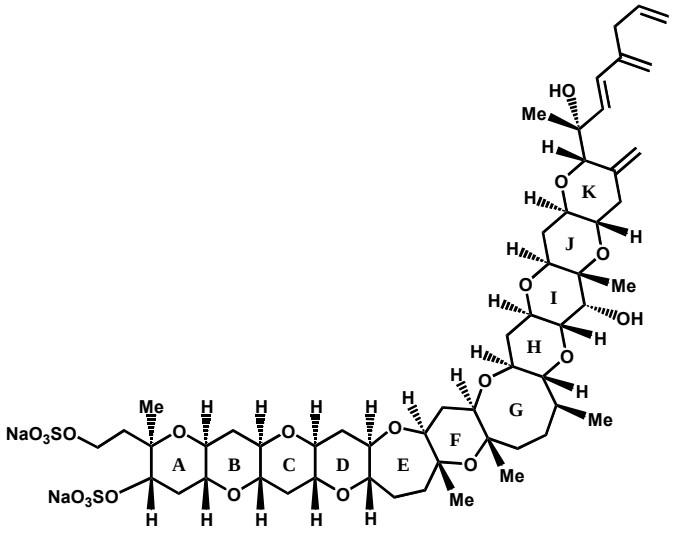
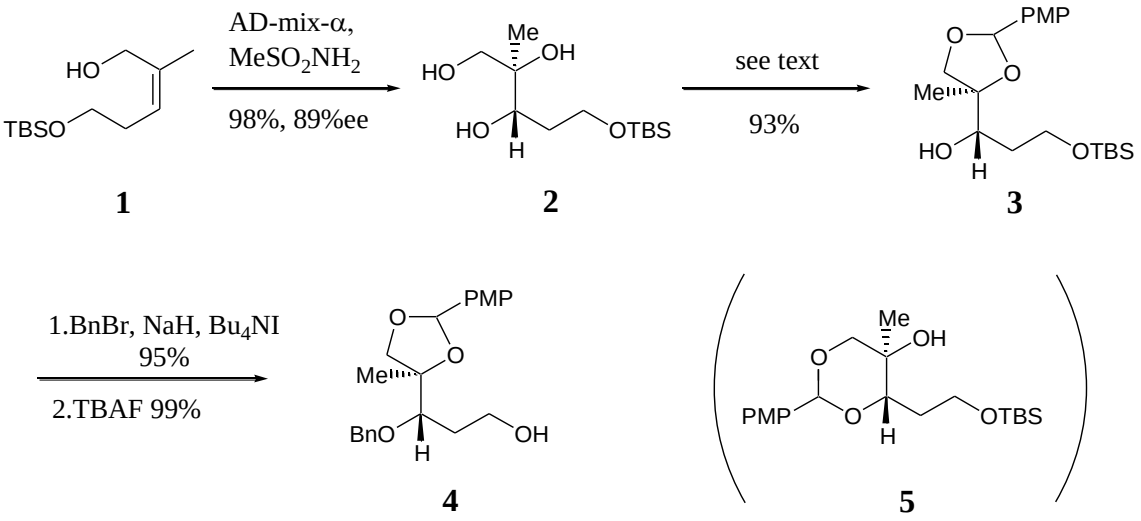


Figure 1. Structure of yessotoxin

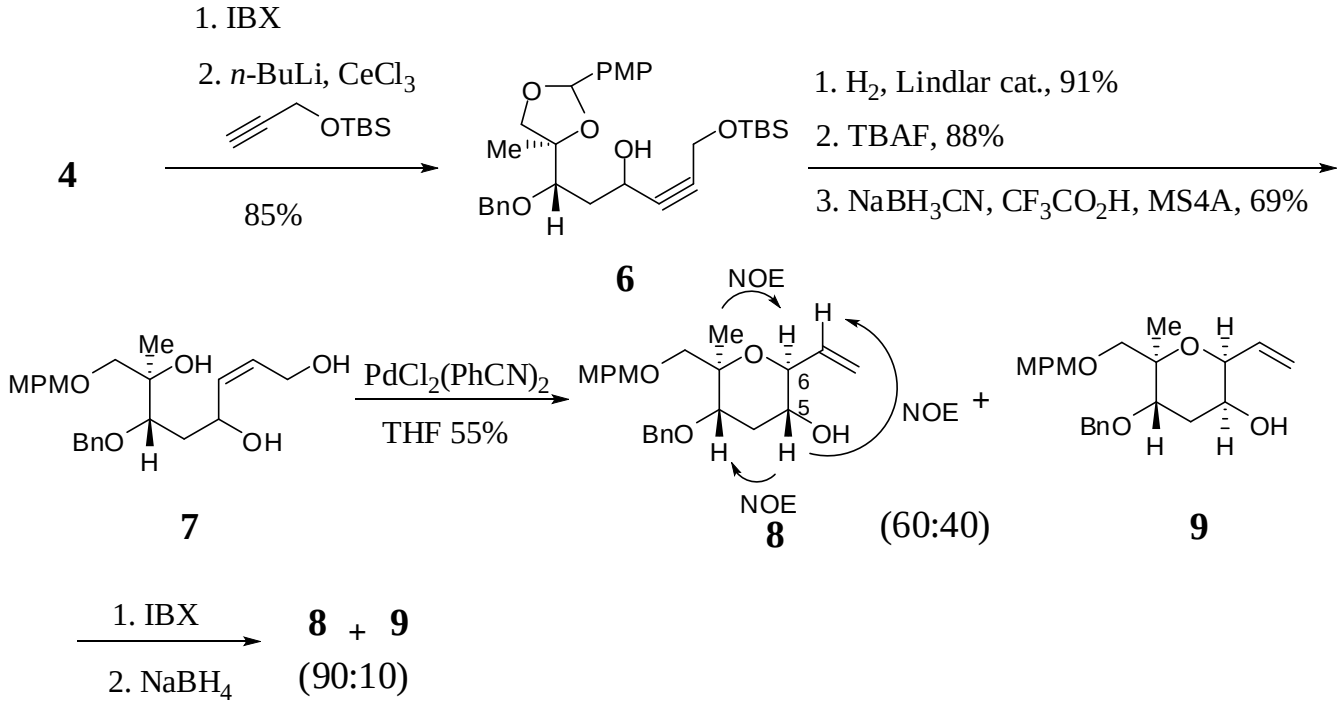
Our starting material was the alcohol (**1**), which was prepared from 1,3-propanediol by 4 steps.[4] Asymmetric dihydroxylation of **1** with AD-mix-α and $MeSO_2NH_2$ gave the triol (**2**) in 98% yield and 89% ee.[5] In next protection step, we examined several conditions. At 0 °C, the protection of the triol (**2**) was selective and was achieved in the presence of 1.3 equivalents of *p*-$MeOC_6H_4CH(OMe)_2$ and a catalytic amount of PPTS in CH_2Cl_2 for 0.5 h to give the acetal (**3**) in 93% yield. However at room temperature, 1,3-acetal (**5**) was obtained in 63% yield. This phenomenon could be due to the kinetic control at 0 °C. The hydroxyl group of **3** was protected with BnBr and TBS protection of the resulting benzyl ether was deprotected by TBAF treatment to afford the alcohol (**4**) in 94% yield (Scheme 1).



Scheme 1

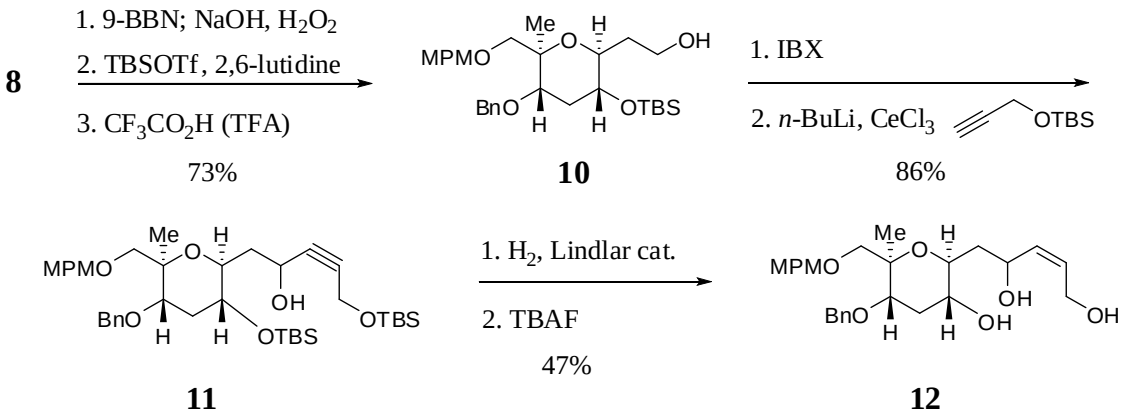
Oxidation of **4** with IBX, followed by continuous addition of cerium acetylide (prepared from *tert*-butyldimethyl(2-propynyloxy)silane with *n*-BuLi and $CeCl_3$) provided the alcohol (**6**) as a diastereomixture in 85% yield. Lindlar hydrogenation of **6**, followed by deprotection with TBAF treatment and regioselective cleavage[6] of the acetal moiety gave the triol (**7**) in 55% yield (3 steps). Next the triol (**7**) was treated with 30 mol% $PdCl_2(PhCN)_2$ in THF at 0 °C to afford the alcohol (**8**) and diastereomer (**9**) on C_5 position in the ratio of 60:40 in 55% yield.

Oxidation of the hydroxyl moiety, followed by reduction with $NaBH_4$ provided the A ring system (**8**) and the diastereomer (**9**) in the ratio of 90:10 (Scheme 2). The A ring system (**8**) was isolated in 73% yield (2 steps) and the stereochemistry of **8** was determined by means of NOE experiments.[7]



Scheme 2

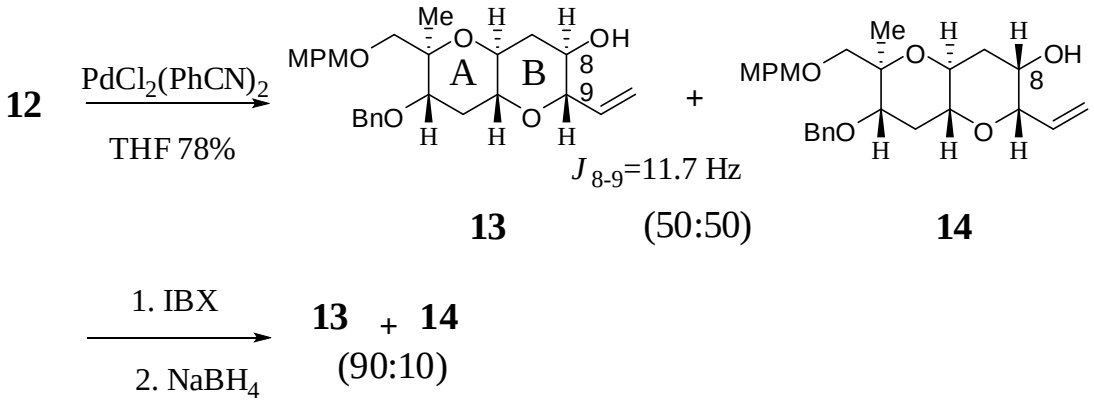
Hydroboration of **8** with 9-BBN, followed by protection of two hydroxyl moeities with TBSOTf, 2,6-lutidine and deprotection of only primary hydroxyl moiety with TFA treatment gave the alcohol (**10**) in 73% yield (3 steps). Oxidation of **10** with IBX, followed by the addition of cerium acetylide gave the alcohol (**11**) as a diastereomixture of 50:50 in 86% yield (2 steps). Lindlar hydrogenation and the following deprotection of TBS protection of **11** with TBAF provided the allylic alcohol (**12**) in 47% yield (2 steps) (Scheme 3).



Scheme 3

The allylic alcohol (**12**) was treated with 30 mol% $PdCl_2(PhCN)_2$ in THF at 0 °C to give the bicyclic compound (**13**) and diastereomer (**14**) in the ratio of 50:50 on C_8 position in 78% yield. Successive

oxidation and reduction of **13** and **14** provided the AB ring system (**13**) and the diastereomer (**14**) in the ratio of 90:10 (Scheme 4). The AB ring system (**13**) was isolated in 49% yield (2 steps) and the stereochemistry of **13** was determined by the coupling constant ($J_{8\text{-}9}$ = 11.7 Hz) of C8-C9 and extensive NMR experiment.[8]



Scheme 4

A plausible mechanism of the Pd(II)-catalyzed cyclization of **7** is shown in Figure 2. Pd π-complex is formed by coordination of $PdCl_2L_n$ with the allylic alcohol, and one of the π-faces of the olefin may be preferentially recognized with the assistance of the adjacent hydroxyl group. The resulting complex may be present as an equilibrium mixture of two structures (**A** and **B**). Conformation **B** is destabilized by non-bonding interaction between the Pd catalyst and Me group. Although conformation **B** is strongly destabilized by A[1,2] strain, conformation **A** is not. Because of these two factors, the overall mechanism can account for the observed predominant formation of **8** and **9**.

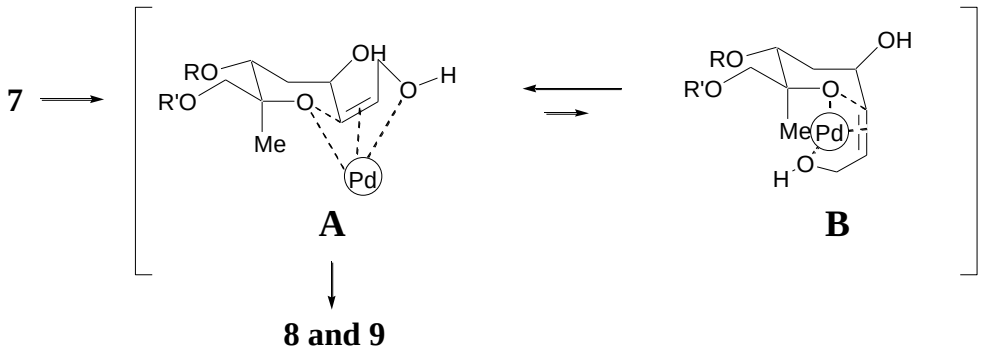


Figure 2

In the case of **12**, conformation **D** would be unfavorable, because of non-bonding interaction between the Pd catalyst and juncture protons. The stereochemical outcome can be explained from conformation **C** (Figure 3).

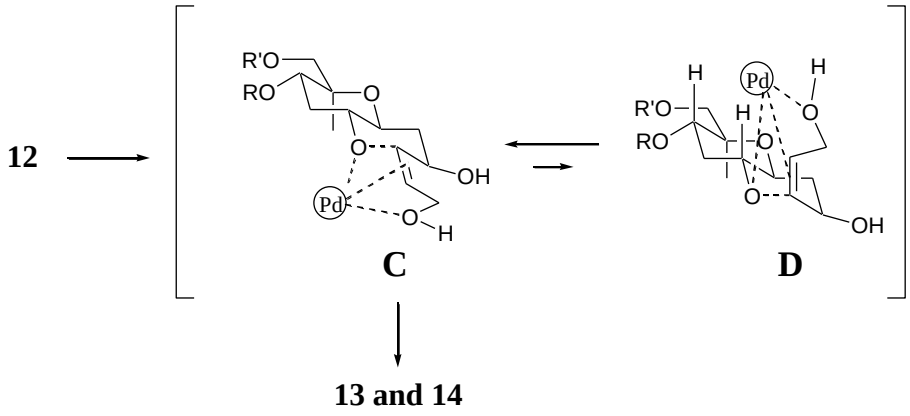


Figure 3

In conclusion, we have synthesized the AB ring system of yessotoxin by means of Pd(II)-catalyzed cyclization. Further studies aimed at total synthesis of yessotoxin are under way in our laboratory.

ACKNOWLEDGEMENTS

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5. Absolute configuration of the triol (**2**) was assigned tentatively by application of the Sharpless mnemonic. See: S. Alvarez, R. Alvarez, and A. R. deLera, *Tetrahedron: Asymmetry*, 2004, **15**, 839. The enantiomeric ratio of the triol (**2**) was determined by ^{1}H NMR analysis of *O*-methylmandelate ester derivatives of **2**.
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7. The selected data for **8**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.32-7.29 (m, 2H), 7.28-7.22 (m, 5H), 6.84-6.82 (m, 2H), 5.8 (ddd, *J* = 16.6, 10.3, 7.0 Hz, 1H), 5.39 (ddd, *J* = 16.6, 1.5, 1.1 Hz, 1H), 5.31 (ddd, *J* = 10.6, 1.1, 0.7 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 3.81-3.76 (m, 1H), 3.77 (s, 3H), 3.70 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.53 (d, *J* = 10.5 Hz, 1H), 3.43 (d, *J* = 10.5 Hz, 1H), 3.33 (ddd, *J* = 12.0, 10.3, 4.8 Hz, 1H), 2.39 (ddd, *J* = 11.9, 4.8, 4.8 Hz, 1H), 1.62 (ddd, *J* = 12.0, 12.0, 11.9 Hz, 1H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ:159.1, 138.5, 136.5, 130.6, 129.4, 128.3, 127.50, 127.48, 119.1, 113.7, 77.5, 74.1, 73.7, 73.2, 71.3, 69.0, 55.2, 32.6, 13.7; IR (neat); 3741-3112, 3340, 1651 cm^{-1}; EIMS *m/z* 398 (M^+); HREIMS calcd. for $C_{17}H_{23}O_5$ (M^+-Bn) 307.1545, found 307.1540.
8. The selected data for **13**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30-7.17 (m, 7H), 6.84-6.83 (m, 2H), 5.84 (ddd, *J* = 17.4, 10.6, 7.5 Hz, 1H), 5.43 (dd, *J* = 17.4, 0.7 Hz, 1H), 5.36 (dd, *J* = 10.6, 0.7 Hz, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 12.1 Hz, 1H), 4.34 (d, *J* = 11.7 Hz, 1H), 3.77 (s, 3H), 3.74 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.54 (dd, *J* = 8.8, 7.5 Hz, 1H), 3.50 (d, *J* = 10.6 Hz, 1H), 3.49-3.44 (m, 1H), 3.41 (d, *J* = 10.6 Hz, 1H), 3.34 (ddd, *J* = 11.4, 9.3, 4.0 Hz, 1H), 3.05 (ddd, *J* = 11.7, 9.3, 4.7 Hz, 1H), 2.37 (ddd, *J* = 14.7, 4.7, 4.7 Hz, 1H), 2.36 (ddd, *J* = 13.9, 4.0, 4.0 Hz, 1H), 1.59-1.51 (m, 2H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.11, 138.41, 135.45, 132.44, 130.89, 130.47, 129.45, 128.81, 128.27, 127.52, 113.68, 83.77, 77.80, 77.22, 74.11, 73.11, 71.18, 69.05, 68.16, 55.22, 23.74, 22.99, 13.88; IR (neat); 3773-3098, 1613 cm^{-1}; EIMS *m/z* 454 (M^+); HREIMS calcd. for $C_{20}H_{27}O_6$ (M^+-Bn) 363.1808, found 363.1794.